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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,450	05/09/2001	Martin F. Yanofsky	19452A002400	6298

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EXAMINER	
BAUM, STUART F	
ART UNIT	**PAPER NUMBER**
1638	11

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,450	YANOFSKY ET AL.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *11,13,17-27,30,31,36,38,51-61,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,14-16,28,29,32-35,37,39-50,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-65 are pending.

2. Applicant's election with traverse of Group I, claims 1-10, 12, 14-35, 37 and 39-65 including SEQ ID NO:2 and 32 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Applicant submit that examination of the claims in Groups I-IV would not create an undue burden. This is not found persuasive because while the search of the prior art for one group may overlap with that of another, they are not co-extensive of each other and thus would be a burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 11, 13, 17-27, 30-31, 36, 38, 51-61, and 64-65 are withdrawn from consideration as being drawn to non-elected inventions.

3. Claims 1-10, 12, 14-16, 28-29, 32-35, 37, 39-50, and 62-63 are examined in the present office action.

Claim Objections

4. Claims 1, 14, 15, 32, 33, 48, and 49 are objected to for reciting non-elected inventions. Applicant is requested to amend the claims to not read on the non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-10, 12, 14-16, 28-29, 32-35, 37, 39-50, and 62-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the recitation of "ectopically" is unclear and not defined. It is suggested to replace "ectopically" with "over-expressed". All subsequent recitations of "ectopically" are also rejected. All subsequent recitations of "ectopically" are also rejected.

In claim 1, the metes and bounds of "gene product" have not been defined. Is Applicant referring to the protein expressed from the complete Ap1 gene or is Applicant referring to a polypeptide with the same function as AP1, and if so, what is the function of the AP1 protein and how does one assay its function to determine the metes and bounds? All subsequent recitations of "gene product" are also rejected.

In claim 1, the recitation "at least 50% identical" should be replaced with "exhibiting at least 50% sequence identity". All subsequent recitations of "at least 50% identical" are also rejected.

In claim 2, the recitation "early" lacks a comparative basis.

In claim 7, the term "modified" is unclear. Applicant needs to explicitly state how the gene regulatory element has been changed and what is the end result of the modification. What is the desired end product of the modification? All subsequent recitations of "modified" are also rejected.

In claim 7, "comprising" should be replaced with "further comprising". All subsequent recitations of "comprising" are also rejected.

In claim 28, line 2, "an" should be replaced with "a".

In claim 29, line 2, "an" should be replaced with "a".

In claim 29, line 2, "is" should be replaced with "encodes".

In claim 32, the term "modulating" is unclear. Applicant needs to explicitly state how the timing of reproductive development has been changed.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. As presently stated, the claim does not result in a modulation of the timing of reproductive development.

In claim 48, line 2, the word "is" should be replaced with "encodes".

In claim 48, line 2, the word "which" should be inserted after the word "product".

In claim 49, line 2, the word "is" should be replaced with "encodes".

In claim 49, the word "comprises" should be replaced with "comprising".

In claim 62, line 2, the word "is" should be replaced with "encodes".

In claim 62, line 2, "an" should be replaced with "a".

In claim 62, line 2, the word "which" should be inserted after the word "product".

In claim 63, line 2, the word "is" should be replaced with "encodes".

In claim 63, line 2, "an" should be replaced with "a".

In claim 63, the word "comprises" should be replaced with "comprising".

Clarification and/or correction are required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10, 12, 14-16, 28-29, 32, 33-50, and 62-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a non-naturally occurring seed plant comprising an two ectopically expressed polynucleotides, one of which encodes an APETALA1 polypeptide exhibiting at least 50% amino acid identity to SEQ ID NO:2 and the other polynucleotide encodes a SEPALATA3 (SEP3) polypeptide exhibiting at least 50% amino acid identity to SEQ ID NO:32, wherein the ectopically expressed polynucleotides comprise a modified gene regulatory element, or a method of modulating the timing of reproductive development in a plant comprising ectopically expressing both above mentioned polynucleotides in a plant.

Applicants do not present a description of domains that are specific to either AP1 or SEP3 nor domains that are important for their proper function. Given the lack of description, one skilled in the art would not be able to identify sequences with less than 100% sequence identity that still maintained the proper activity. The claims recite polynucleotides encoding polypeptides exhibiting at least 50% identity to either SEQ ID NO:2 or 32, but Applicants have not disclosed a representative number of species as encompassed by the claims. The claims encompass mutants and allelic variants and thus imply that structural variants exist in nature, yet no structural variants have been disclosed. The implication is that there are genes and corresponding proteins other than those disclosed which exist in nature, but the structure thereof

is not known. Thus, there is insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine such mutants and allelic variants from other plants and organisms, absent further guidance. Therefore, the written description requirement is not satisfied. Therefore, one skilled in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention. (see Written Description Requirement published in Federal Register/Vol.66, No. 4/ Friday, January 5, 2001/Notices; p. 1099-1111).

Scope of Enablement

7. Claims 1-10, 12, 14-16, 28-29, 32, 33-50, and 62-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-naturally occurring seed plant and a method for decreasing the amount of time it takes for a plant to switch from vegetative growth to reproductive development comprising introducing into a plant two nucleic acids, each one operably linked to the 35S CaMV promoter, wherein the respective nucleic acid molecules encode two corresponding polypeptides comprising AP1 of SEQ ID NO:2 and SEP3 of SEQ ID NO:32 wherein the over-expression of both nucleic acid molecules encoding the respective polypeptides results in an increase in the expression of the respective nucleic acids and produces a plant whose transition to reproductive development occurs before a wild-type plant not expressing said nucleic acid molecules, does not reasonably provide enablement for claims broadly drawn to a non-naturally occurring seed plant and a method for decreasing or increasing the amount of time it takes for a plant to switch from vegetative growth to reproductive development both of which comprising introducing into a plant two nucleic acids, each one operably linked to a modified gene regulatory element, wherein the expression of the

respective nucleic acid molecules encoding two corresponding polypeptides exhibiting at least 50% sequence identity to AP1 of SEQ ID NO:2 or SEP3 of SEQ ID NO:32 is increased or decreased in a tissue compared to a wild-type plant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *In re Wands* factors (858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

It cannot be predicted by one of skill in the art that nucleic acids encoding a polypeptide exhibiting at least 50% sequence identity to either AP1 of SEQ ID NO:2 or SEP3 of SEQ ID NO:32 will encode a protein with the same activity as SEQ ID NO:2 and 32. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many

amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by McConnell et al (2001, Nature 411 (6838):709-713), who teach that the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain. This change renders the protein constitutively active and therefore creates a dominant mutation which has a drastic alteration in phenotype compared to wild-type *Arabidopsis* plants.

Applicants have claimed plants and a method, both of which comprise introducing into a plant two nucleic acid sequences that encode proteins exhibiting at least 50% sequence identity to the reference SEQ ID NO:2 or 32. The state of the art teaches that the function of MADS domain proteins are sensitive to amino acid changes within the protein. This is exemplified by Krizek et al (1996, Proc. Natl. Acad. Sci. 93:4063-4070) who teach that the *Arabidopsis* MADS domain proteins AP1, AP3, PI, and AG are involved in specifying floral organ identity and all possess the conserved MADS, K, and L domains. Krizek et al performed experiments in which the before mentioned domains were swapped from one gene to another and then transformed into a plant to see if the genes with the swapped domains still functioned as the wild-type genes. They report that the "AG MADS box and L regions were sufficient in an AP1 context to specify AG function but were not sufficient in an AP3 context" (page 4069, right column, 3rd paragraph).

They conclude by stating "residues in the K domain of AG contribute to its functional specificity" (*ibid*). Their results demonstrate that functional specificity depends on more than just one conserved region.

The Applicants are claiming a plant comprising a modified gene regulatory element. Applicants have not disclosed how the regulatory elements are modified or for what purpose. It is known in the art that the spatial and temporal expression of AP1 and SEP3 is crucial for the transition to flowering to occur, both in wild-type plants and in Applicants' invention. Therefore, having a modified regulatory element that does not express in the correct spatial and temporal pattern will not achieve the desired result. The state of the art teaches using pieces of a promoter that do not contain the full compliment of cis-acting elements, will not produce the expression profile as observed using the whole promoter fragment. Kagaya et al (1995, Mol. Gen. Genet. 248 :668-674) teach the rice chloroplastic aldolase promoter contains two elements, one of which acts as a negative element while the other acts as a positive element that confers developmentally regulated mesophyll cell specific expression. Removal of either of these regions changes the normal expression pattern (page 670, left column). Kagaya et al also teach that the promoter contains an element that serves as a target for light induction (abstract).

Benfey et al (1990, Science 250:959-966) teach that the 35S CaMV promoter consists of domains that individually regulate spatial expression within plants. "The combination of each of the five B subdomains with domain A results in an expression pattern that differs from that of the individual subdomains or domain A" (page 961, left column, 2nd paragraph). In other words, deleting a required domain will jeopardize the proper spatial and temporal expression pattern. In addition, Benfey et al (1989, EMBO J, 8(8):2195-2202; page 2200, left column 2nd paragraph)

teach that not only are the promoter domains important for specifying proper spatial and temporal expression but that when all domains were present, the quantity of expression increased.

Non-coding nucleic acid sequences that exhibit base pair deletions, substitutions or rearrangements, cannot be expected to maintain their promoter or enhancer activity. Izawa et al (1993, J. Mol. Biol. 230 :1131-1144) teach the nucleotides flanking the G-box (CACGTC) and C-box (GACGTC) hexameric cores were shown to affect protein binding activity and specificity of bZIP transcription factors (page 1132, bottom of right column; page 1134, bottom of left column). Hao, et al (1998, The J. of Biological Chemistry 273 (41): 26857-26861) investigated the binding activities of ethylene-responsive element-binding proteins (EREBP) to their cis-element GCC box (AGCCGCC). Creating base-pair substitutions within the GCC box modulates binding specificity, implying that different positions within the GCC box are important for differential binding by different EREBP's, in particular, substituting T's for the two G's eliminates binding completely (*supra*, pages 26857, abstract and 26860, left column, 2nd paragraph).

Applicants are not enabled for decreasing the expression of either one or both of the previously mentioned nucleic acid sequences as well as increasing the time of reproductive development when compared to a wild-type plant. Applicants are only enabled for expression of AP1 of SEQ ID NO:2 and SEP3 of SEQ ID NO:32, both of which are in sense orientation, for the purpose of increasing the expression of both nucleic acids. Applicants have not demonstrated that co-suppression will work in the present invention nor have they taught or disclosed how one skilled in the art would identify a plant in which one or both of the previously

specified nucleic acid sequences is being affected by co-suppression. Applicants have not taught or disclosed the phenotype of a plant in which one or both previously mentioned sequences are being affected by co-suppression.

Even though Applicants did not use or claim plants or methods using antisense technology, the mechanism of RNA degradation while using co-suppression is the same as the RNA degradation mechanism associated with antisense technology. The state of the art teaches using sequences exhibiting below a 100% sequence identity as compared to a reference sequence produces unpredictable RNA degradation results. Moonan et al (2002, Journal of Virology 76(3):1339-1348) teach " sugarcane plants expressing untranslated viral capsid sequences of *Sorghum mosaic virus* strain SCH, challenged with SrMV viruses of strains SCM and SCI and *Sugarcane mosaic virus* strain, show various levels of virus resistance that correlated with the percentage of sequence identity of the transgenes to the sequence of the challenging virus" (page 1347, 1st paragraph, right column). Therefore, the protection achieved using sequences that exhibited less than 100% sequence identity to the respective viral gene resulted in an inferior viral protection.

Given the unpredictability of using sequences that exhibit less than 100% sequence identity to AP1 of SEQ ID NO:2 or SEP3 of SEQ ID NO:32 to increase or decrease the expression of the respective nucleic acid sequences in plant tissue when compared to a wild-type plant, for the reasons stated above; given the unpredictability of using a modified gene regulatory element to express the respective sequences for the reasons stated above; given the unpredictability of using the specified sequences to decrease the expression of the respective sequences or produce a phenotype in which the time to flowering in prolonged when compared

to wild-type plants for the reasons stated above; given the lack of guidance or examples for using sequences that exhibit less than 100 % sequence identity to the previously mentioned sequences for the purpose of increasing or decreasing the expression of the respective sequences or for creating plants with an increased time to flowering when compared to a wild-type plant; given the lack of guidance or examples for using a modified gene regulatory element for the reasons stated above; given the state of the art that teaches MADS box transcription factor are sensitive to changes in as little as one amino acid residue, and that the mechanism for gene silencing when using either antisense or co-suppression is very much affected by percent identity of the sequence that is transformed into a plant and the respective endogenous sequence; and given the claim breadth, it would require undue experimentation by one skilled in the art to make and/or use the claimed invention.

8. No claims are allowed. A plant or method comprising expression of both nucleic acid sequences encoding AP1 and SEP3 polypeptides of SEQ ID NO:2 and 32 respectively are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest a plant or method both of which comprising the expression of both nucleic acid sequences encoding AP1 and SEP3 polypeptides of SEQ ID NO:2 and 32, respectively.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart Baum whose telephone number is (703) 305-6997. The examiner can normally be reached on Monday-Friday 8:30AM – 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 or (703) 305-3014 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist, who may be contacted at 308-0196.

Stuart F. Baum Ph.D.

February 22, 2003

PHUONG T. BUI
PRIMARY EXAMINER 2/24/03